LONG-TERM EFFECTS OF NALBUPHINE ER TABLETS IN HEMODIALYSIS PATIENTS WITH UREMIC PRURITUS: A MULTICENTER OPEN-LABEL TRIAL

Jayant Kumar[1], Paul Crawford[2], Vandana Mathur[3], Thomas Sciascia[4]

[1]Renal Medicine Associates, NM, [2]Research by Design, IL, [3]MathurConsulting, CA, [4]Trevi Therapeutics, CT USA

BACKGROUND

- A recently conducted study of 73,000 United States dialysis patients reported that 60% have pruritus and that 30% are moderately to extremely bothered by it[1].
- Uremic pruritus is associated with significant decreases in quality of life (QoL), sleep, and greater use of IV antibiotics, ESA, and iron[1].
- The pathogenesis of uremic pruritus may involve endogenous κ/μ opioid ligand ratio imbalance[2,3].
- Nalbuphine ER tablets (NAL) are a κ-opioid agonist/μ-opioid antagonist being developed for chronic pruritic conditions.

METHODS

- This was a multicenter open-label single-arm study that was the extension of a randomized controlled trial of 373 hemodialysis patients who were randomized (1:1:1) to NAL 60 mg (n=128) or 120 mg (n=120) or placebo (n=125) BID and treated for 8 weeks. The parent study met its primary efficacy endpoint, demonstrating that NAL 120 mg resulted in a significant reduction in itching intensity compared with placebo.
- After a 2-week washout period from the parent study, patients who completed the parent study who had at least one numerical rating scale score (NRS) >2.0 (0 [no itch] -10 [worst possible itching]) at the extension study baseline visit were eligible to receive open-label NAL for up to 24 weeks [**Figure 1**]. Patients completing the parent study whose NRS scores were both ≤ 2 were entered into an Observation Period and were eligible to receive open-label treatment if the NRS score increased to >2.0 at any point during the up to 24 week Observation Period [**Figure 1**].
- NAL was titrated during the first 3 weeks of treatment to effect and tolerability and the dose was then maintained. Background antipruritic medications were allowed to be continued.
- The primary objective of the study was to evaluate safety of NAL over a 24-week treatment period. The primary secondary objective was to evaluate changes in itching intensity (NRS) and other patient-reported outcomes.

RESULTS

Figure 1: Study Schematic

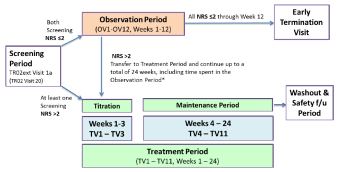


Figure 2: Itching Reduction over Time

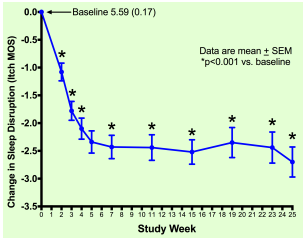
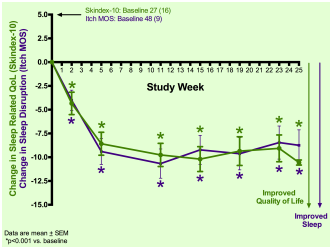


Table 1: Baseline Characteristics

Characteristic	N (%)
Treated	167
Age (years)	53 (12)
% Male	55%
%White/African American	45/53%
Duration on dialysis	5.0 (4.4) years
AVF/AVG/catheter	71/19/8%
Baseline NRS	
0 to <4	21%
≥ 4 to <7	49%
≥ 7	31%

Figure 3: Improved Quality of Life and Sleep over Time



RESULTS, continued

- 184 patients were enrolled, of whom, 167 (91%) received treatment **(Table 1**) and 17 were entered into the Observation Period and never received treatment
- 101 patients (61%) completed 24 weeks of treatments and 66 prematurely discontinued (19 due to adverse events, 16 due to consent withdrawal)
- The mean Worst Itching Intensity (0 = no itching; 10 = worst possible itching) decreased significantly from baseline to all measured time points (p<0.001) **(Figure 2)**
- The mean itching-related quality of life (Skindex-10) and itching-related sleep disruption improved significantly from baseline to all measured time points (p<0.001) **(Figure 3)**
- During this 24 week study, 32.3% of patients experienced serious adverse events, of which, 4 (2.4%) had events that were related to the study drug: headache [n=1], constipation [n=2], and gastritis [n=1]
- The most common adverse events (>10%) were nausea (26%) and vomiting (20%)

CONCLUSIONS

- Long-term treatment with NAL was associated with significant and sustained reductions in itch intensity and improved itch-related sleep disruption and quality of life.
- The findings from this study, taken together with the parent randomized, double-blind placebo controlled trial suggest that NAL could be an effective chronic treatment for uremic pruritus.

REFERENCES

1. Ramakrishnan International J Nephrol Renovas Dis 2014
2. Kumagai *In* Itch Basic Mechanisms and Therapy 2004
3. Wang and Yosipovitch Int J Dermatology 2010